## REMARKS

This is a request to withdraw the appeal and reopen prosecution before the Examiner pursuant to 37 C.F.R. § 1.114(d). Further, the following amendments and remarks are in response to the Official Action mailed July 28, 2008. Claims 1-5 and 17-45 are pending in the present application. Claims 2, 4, 5, 17, and 32-45 are canceled herein without prejudice or disclaimer. Claims 1, 3, 18, 22, 25 and 29 are amended herein for clarity to more particularly define the invention. Support for the amendment of claims 1 and 3 to recite "an allele of a single nucleotide polymorphism" can be found throughout the specification, including, at least for example, on page 21, lines 10-25. Support for the amendment of claims 22 and 29 to recite a subject "for whom identification of an increase or decrease in warfarin sensitivity is desired" can be found throughout the specification, including at least for example, on page 14, lines 17-20, page 15, lines 8-17, and page 16, lines 14-21. Support for the amendment of claims 18 and 25 to recite "wherein said segment is in a noncoding region of the nucleotide sequence" can be found throughout the specification, including at least for example, on page 20, lines 15-23, page 21, lines 4-6, page 28, Table 1, and page 29, Table 2. It is believed that no new matter is added by these amendments and their entry and consideration are respectfully requested. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

### I. Recordation of Interview Summaries

A. To record the Interview Summary mailed on March 9, 2009 regarding the above-referenced patent application, applicants concur that the Interview Summary accurately reflects the substance of the telephone interview that took place on March 4, 2009, in which Examiner Jehanne S. Sitton and applicant's representative, Dr. Mary Miller, participated.

B. To record the Interview Summary mailed on March 24, 2009 regarding the above-referenced patent application, applicants concur that the Interview Summary accurately reflects the substance of the telephone interview that took place on March 17, 2009, in which Examiner Jehanne S. Sitton and applicant's representative, Dr. Mary Miller, participated.

**II. Rejection under 35 U.S.C. § 112, first paragraph**

**A.** The Office Acton states that claims 1, 3-5, 17, 21, 28, 35, and 42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

As an initial point, applicants note that claims 4, 5, 17, 35, and 42 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

As set forth in the previous response, applicants respectfully submit that under an analysis of the claimed invention pursuant to the factors set forth in *In re Wands*, the present invention is indeed demonstrated to be enabled and therefore this rejection is traversed. This analysis is reiterated below.

*Amount of guidance and working examples.*

Claim 1 recites a method of identifying a human subject having an increased sensitivity to warfarin, wherein a therapeutic dose of warfarin for the subject is lower than a therapeutic dose of warfarin for a normal subject, comprising detecting in the subject the presence of an allele of a single nucleotide polymorphism in the VKOR gene, wherein the allele of the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject having increased sensitivity to warfarin. Claim 3 recites a method of identifying a human subject having an increased sensitivity to warfarin, comprising: a) correlating the presence of an allele of a single nucleotide polymorphism in the VKOR gene with increased sensitivity to warfarin; and b) detecting the allele of the single nucleotide polymorphism of step (a) in the subject, thereby identifying a subject having increased sensitivity to warfarin.

Claims 21 and 28 depend from claims 18 and 25, respectively. Thus, claim 21 recites a method of amplifying a segment of a VKOR genomic nucleotide sequence, wherein said segment is in a noncoding region of the nucleotide sequence, comprising: a) choosing a first oligonucleotide primer from the 3′ end of the nucleotide sequence of SEQ ID NO:8; b) choosing a second oligonucleotide primer from the 5′ end of the nucleotide sequence of SEQ ID NO:8; c) adding said first primer and said second primer to a nucleic acid sample; and d) amplifying a segment of the VKOR genomic nucleotide sequence defined by the first primer and the second primer, wherein said segment is in a noncoding region of the nucleotide sequence and further wherein the amplified segment of step (d) comprises an allele of a single nucleotide polymorphism that is correlated with increased sensitivity to warfarin. Claim 28 recites a

method of amplifying a segment of a VKOR genomic nucleotide sequence, wherein said segment is in a noncoding region of the nucleotide sequence comprising: a) choosing a first oligonucleotide primer from the nucleotide sequence of SEQ ID NO:8; b) choosing a second oligonucleotide primer from the nucleotide sequence of SEQ ID NO:8 that differs in nucleotide sequence from the first oligonucleotide primer; c) adding said first primer and said second primer to a nucleic acid sample; and d) amplifying a segment of the VKOR genomic nucleotide sequence defined by the first primer and the second primer, wherein said segment is in a noncoding region of the nucleotide sequence and further wherein the amplified segment of step (d) comprises an allele of a single nucleotide polymorphism that is correlated with increased sensitivity to warfarin.

With the teachings of the present specification, one of skill in the art would readily recognize that the methods of claims 1 and 3 can be carried out in human subjects of any race or ethnicity and are based on having the knowledge of which alleles of single nucleotide polymorphisms (SNPs) of the VKOR gene are correlated with increased sensitivity to warfarin pursuant to applicants' discovery and teachings as to how to detect such alleles. Further, one of skill in the art would readily recognize that the amplification methods of claims 21 and 28 were well known in the art at the time the present invention was made and that they also are based on having the knowledge of which alleles of SNPs of the VKOR gene are correlated with increased sensitivity to warfarin pursuant to applicants' discovery. Such knowledge is accessible to the ordinary artisan without undue experimentation. The specification provides working examples with actual reduction to practice of the methods of the present invention and provides more than ample guidance for one of skill to identify any SNP allele and to correlate any SNP allele in the VKOR gene with increased warfarin sensitivity without undue experimentation. It is not necessary that the specification teach each and every SNP allele and whether it is correlated with increased sensitivity to warfarin for one of skill to carry out the methods of this invention. Nor is it necessary that one of skill in the art be able to predict an association between a particular SNP allele and warfarin sensitivity because the present specification clearly teaches how to identify them.

Single nucleotide polymorphisms are well known in the art and are readily identified in any particular gene one chooses to analyze. In fact, it is noted that many of the SNPs of the

VKOR gene had been identified at the time the present invention was made although their relationship with the VKOR gene was not known until the present invention. Once the present inventors identified the VKOR gene, these SNPs became available for analysis to evaluate whether their alleles correlate with warfarin sensitivity. Further, determining warfarin dosages is well known in the art and correlating SNP alleles with particular phenotypic traits is routine once the SNPs are identified. Thus, with the teachings of the specification, including the teaching of the VKOR gene sequence and the exemplary SNP analyses, it would **not** be undue to test the alleles of the 25 particular SNPs in the VKOR gene as described in the 2005 Geisen et al. publication or any other allele at a SNP site identified in the VKOR gene. Thus, similar to the holding of the court in *In re Wands*, "...all of the methods needed to practice the invention were well known." *Id.*, 8 USPQ2d at 1406.

To expound on the fact that correlating SNP alleles with particular phenotypic traits is well known, applicants also provided in the previous response, dated November 30, 2007, a list of **15** publications which, in addition to those cited by the Examiner (i.e., Rieder et al., Oldenberg et al., Rost et al.), provide more than ample evidence that such correlation methods were well known at the time of the applicants' invention. Indeed these publications show how such methods were routine, particularly for correlating alleles of SNPs in the VKOR gene with warfarin sensitivity, once the applicants had identified the VKOR gene and shown that SNP alleles in the VKOR gene could be correlated with warfarin sensitivity. Thus, these publications evidence the fact that once the present applicants identified the VKOR sequence, disclosed it as such and correlated changes as minor as a SNP allele with warfarin sensitivity, numerous other groups were readily able to find and report other SNP alleles associated with warfarin sensitivity. Therefore, it is clear that once the present inventors identified the VKOR gene, numerous previously uncharacterized SNPs became available to those of skill in the art, as is evidenced by the large number of publications of studies that followed the present inventors' identification of the VKOR gene.

For at least the reasons provided above, applicants have demonstrated that the *Wands* factors regarding the amount of guidance, available not only in the present specification but also in the art, as well as the presence of working examples of the claimed invention, weigh in the applicants' favor.

*The nature of the invention and the breadth of the claims*

The Examiner cites *Mycogen Plant Sci., Inc. v. Monsanto Co.* (243 F.3d 1316 1330 (Federal Circuit 2001)) to support her determination that the present invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology."

In response, applicants point out that although the biological sciences have been categorized as "unpredictable," the courts have long and repeatedly emphasized that the issue is not predictability *per se*, but the type of work and experimentation acceptable in the particular field, or fields, of the invention. For example, in *In re Angstadt,* the Court of Customs and Patent Appeals cautioned that:

> "If [our prior decision stands] for the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction,* whether the claimed product will be obtained,.... then *all* 'experimentation' is 'undue', since the term 'experimentation' implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the patent act...."

*In re Angstadt,* 537 F. 2d 498, 503, 190 USPQ 214, 218-219 (CCPA 1976).

The court in *Angstadt* went on to emphasize that "...the key word is 'undue,' not 'experimentation'." *Id.* at 504, 190 USPQ at 219. Thus, it is clear that even in an "unpredictable" art, an invention can be enabled, provided that the amount of experimentation required to carry out the invention is not undue.

Applicants respectfully point out that claims 1 and 3 are directed specifically to human subjects, and claims 1, 3, 21 and 28 are directed specifically to 1) a defined phenotype of increased sensitivity specifically to the drug, warfarin, and 2) a defined genotype of an allele of a SNP of the VKOR gene that is correlated with the defined phenotype according to well known and standard statistical methods. The invention as claimed is therefore quite specific in scope and definition and is not overly broad or unclear and it is apparent that the nature of the invention and breadth of the claims are such that one of skill in the art could carry out the methods as claimed herein without undue experimentation. Thus, both of these factors weigh in favor of the applicants.

*State of the art and predictability of the art*

The Examiner maintains that the unpredictability in the technology associated with the present invention is high and that although there is a large body of knowledge in the prior art related to polymorphisms in general and their association with diseases or disease states, the art is highly unpredictable with regard to functionality of polymorphism sites in genomic DNA. In further support of the contention that the association between any given polymorphism in a gene and a given disorder is unpredictable, the Examiner cites Lucentini et al. ( *The Scientist* December 20, 2004, page 20) and Hegele et al. (*Arterioscler. Thromb. Vasc. Biol.* 22:1058-1061 (2002)). Applicants respectfully point out that these articles discuss problems related to associations made for diseases such as atherosclerosis, schizophrenia and cancer and have no relevance to the present invention directed to warfarin sensitivity and the VKOR gene. Further and most importantly, applicants note that even though the relationship between the VKOR gene was reported by the present inventors in 2004, no reports of non-replication or refutation have followed. In fact, follow-up research as exemplified by at least the 15 references provided in the previous response has continued to confirm the link between alleles of SNPs in the VKOR gene and warfarin sensitivity.

Applicants note that even in arts defined to be "unpredictable," the standard for enablement is still whether undue experimentation would be required to carry out the invention as claimed. As the applicants, as well as those following in their footsteps, have amply demonstrated, not only were all of the methods needed to practice the claimed invention well known in the art, but the artisan has been proven to be fully capable of carrying out the methods of this invention without undue experimentation, as can be seen by the large number of scientific groups who have subsequently correlated SNP alleles of the VKOR gene with warfarin sensitivity. Thus, the Examiner's broad generalizations about the unpredictability of the functionality of polymorphic sites in genomic DNA and her citation of Lucentini et al. and Hegele et al. (which describe totally unrelated gene polymorphisms and totally unrelated phenotypes) are not relevant to the present invention (similar to the citations to Hacker et al. and Pennisi et al.; Office Action, pages 6-7). Most importantly, the Examiner fails to take into consideration the applicants' contribution to the art with the identification of the VKOR gene, and the applicants' teaching of methods of correlating alleles of VKOR SNPs with warfarin

sensitivity and identifying subjects with increased sensitivity. The present inventors' contribution to the field of warfarin therapy is invaluable because it provides clinicians with a previously unavailable tool for identifying a subject having increased warfarin sensitivity, allowing them to prescribe an appropriate dose of warfarin that will not be detrimental (and possibly even lethal) to the subject.

Furthermore, the Examiner's comment that not all SNP alleles would be predictive of warfarin sensitivity fails to demonstrate a lack of enablement of the present invention. As applicants have amply demonstrated, one of skill in the art was adequately armed, at the time of this invention, to carry out the claimed methods without undue experimentation. Moreover, it is well established that the presence of inoperative embodiments within the scope of a claim does not necessarily render the claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art; i.e., without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.* 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). It is readily apparent, from the discussion and evidence provided herein, that one of skill in the art could and did carry out the methods of the present invention and identify SNP alleles of the VKOR gene that are correlated with increased warfarin sensitivity, as well as identify SNP alleles in the VKOR gene that are not correlated with increased warfarin sensitivity with expenditure of no more effort than is normally required in the art.

*Relative skill of those in the art*

The applicants concur with the Examiner's assessment that the level of skill in the art is high and in view of the added teachings provided in the applicants' disclosure, it would be well within the realm of capabilities and knowledge of one of skill in the present art to carry out the methods of the present invention with nothing more than routine experimentation. Thus, with regard to skill in the art, applicants submit that this factor also weighs in favor of applicants.

*Quantity of experimentation*

Finally, the Office Action provides an analysis of the present invention pursuant to the *Wands* factor regarding the quantity of experimentation necessary to carry out the claimed invention. Specifically, the Action states that to practice the invention as broadly as it is

claimed, the skilled artisan would have to perform a large study of cases and controls in different human populations to determine whether the C at position 2581 of SEQ ID NO:11 was predictably associated with warfarin sensitivity as well as characterize additional sequences within the VKORC1 gene and determine if they are predictably associated with warfarin sensitivity, as well as determining whether the polymorphisms are so associated in any population or whether the association is population specific. Presumably, it is the Examiner's conclusion that such experimentation would be replete with trial and error experimentation, with the results of each analysis being unpredictable, and that such experimentation is considered undue.

With regard to the quantity of experimentation necessary to carry out the claimed invention, applicants note that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976). In *Wands*, claims to antibodies that required a screening procedure to isolate the desired hybridoma cells from an enormous number of other cells present in the reaction mixture were held to not require experimentation that was "undue." *Id.* at 1406. The amount of effort required to make the antibodies was "not excessive." *Id.* at 1407. Similarly, as the applicants have noted previously, all of the methods needed to carry out the claimed invention were known at the time of this invention and the level of skill of those in this art is deemed to be high. Thus, applicants submit that the experimentation needed in the case of the presently claimed invention is not only routine in the art but that the instant specification provides more than sufficient guidance with respect to the direction in which the experimentation should proceed.

Furthermore, not only does the specification as filed provide more than ample guidance to carry out the methods of this invention, contrary to the assertion in the Office Action, the specification includes an actual reduction to practice of the claimed invention. The methods provided in the present specification as well as those available in the art at the time of this invention are straightforward and routine and there is no evidence to support a statement that identifying a subject's sensitivity to warfarin, identifying SNPs in the VKOR gene of the subject

and correlating the presence of a SNP allele in the VKOR gene with the subject's warfarin sensitivity would "...be replete with trial and error experimentation." In fact, the evidence that numerous other groups have successfully carried out the methods of this invention once the VKOR gene was identified is evidence contrary to this assertion. Also, the only negative teachings in the prior art upon which the Examiner appears to rely are directed to unrelated genes and unrelated disorders. Thus, the performance of "a large study of cases and controls in different human populations" to identify the SNP alleles of this invention would not only be considered by one of skill in the art to be routine in theory; it has also been demonstrated to be routine in practice, as readily evidenced by the large number of studies that have been published that specifically describe carrying out the methods of this invention using routine procedures. Thus, the only conclusion to be drawn from such evidence is that any experimentation associated with the methods of this invention is routine and certainly not undue.

Finally, applicants note that the issue of enablement was recently addressed in the precedential decision by the Board of Patent Appeals and Interferences in *In re Kubin* (Appeal No. 20070819; 83 U.S.P.Q 2d 1410 (Bd. Pat. App. & Interf. 2007); *In re Kubin*, 2008-1184, Serial No. 09/667,859 (Fed. Cir. 2009)). In *Kubin,* the claims at issue were directed to isolated nucleic acids encoding polynucleotides that are at least 80% identical to a specific sequence of a Natural Killer Cell Activation Inducing Ligand (NAIL) polypeptide. The Examiner rejected the claims for lack of enablement on the basis that no working examples of polypeptides with 80% identity were provided and that there were examples in the literature of even one amino acid change in a protein resulting in a different function. The Board reversed the rejection, noting that although molecular biology was generally understood to be an unpredictable art at the time the *Kubin* invention was made, the level of skill in the art was high and the methods needed to practice the invention were well known and routine in the art. The Board specifically stated that "[t]he amount of experimentation to practice the full scope of the claims might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." (*In re Kubin,* 83 U.S.P.Q 2d at 1416).

Similar to the facts in *Kubin,* the methods for practicing the full scope of the present invention were well known and routine at the time the application was filed and were also clearly set forth in the specification. Thus, the skilled artisan could have readily carried out the methods

of identifying a human subject having an increased sensitivity to warfarin based on the disclosure of the present application and what was known in the art at the time the application was filed.

Applicants note that the claims in *Kubin* are directed to an isolated nucleic acid sequence itself, which could encompass brand new isolated or synthesized nucleic acid sequences. In comparison, the present claims are directed to methods of identifying a subject having increased sensitivity to warfarin based on detecting in the subject the presence of an allele of a SNP in a specific nucleic acid sequence from the patient, the VKOR gene, wherein the allele of the SNP is correlated with increased sensitivity to warfarin. Thus, the presently claimed invention presents an even easier case than *Kubin* for concluding that the invention is enabled for the full scope of the claims.

Thus, the *Kubin* decision supports the applicants' contention that given the high level of skill in the art and the level of guidance present in the application in combination with what was known in the art, one of skill in the art would not have been required to perform undue experimentation to practice the presently claimed invention.

In conclusion, applicants respectfully point out that in a determination of whether the enablement requirement is satisfied, the Examiner must consider all the evidence related to each of the above eight factors and any conclusion of non-enablement must be based on the evidence as a whole. *In re Wands*, at 737, 740, 8 USPQ2d, at 1404, 1407. For the present invention, when the evidence as a whole is considered, it is apparent that the methods of the claimed invention do not require undue experimentation, and thus claims 1, 3, 21 and 28 satisfy the requirement for enablement. Applicants therefore respectfully request that this rejection be withdrawn.

**B.** The Office Action states that claims 1, 3-5, 17, 21, 28, 35 and 42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

As an initial point, applicants note that claims 4, 5, 17, 35, and 42 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

As noted above and in the previous response, the applicants have described an actual reduction to practice of the claimed invention. The specification provides a specific example of the methods of claims 1, 3, 21, and 28 in the Examples section on pages 19-22, wherein

protocols are described in which subjects were evaluated for their sensitivity to warfarin, DNA samples from the subjects were analyzed for the presence of known SNP alleles and statistical analyses were carried out to identify alleles associated with increased or decreased sensitivity to warfarin.

Applicants note that in the Office Action it is stated that the claims encompass a large genus of single nucleotide variants, including deletions, substitutions, and insertions at any site within the VKORC1 gene and that such a genus includes a large number of polymorphisms and mutations for which no adequate written description is provided in the specification. Applicants respectfully point out that the rejected claims are not directed to a genus of nucleotide variants; rather claims 1 and 3 provide a method of identifying a subject having an increased sensitivity to warfarin by detecting in the subject an allele of a SNP in the VKOR gene correlated with increased sensitivity to warfarin and claims 21 and 28 recite a method of amplifying a segment of a VKOR genomic nucleotide sequence, wherein the segment is in a noncoding region of the nucleotide sequence, and wherein the amplified segment comprises an allele of a SNP that is correlated with increased sensitivity to warfarin. Thus, claims 1, 3, 21 and 28 are each directed to a method and not to any particular nucleotide variant.

Furthermore, multiple SNPS in the genomic sequence that is identified in the present application as the VKOR gene were known in the art as of the effective filing date of the present application. With the identification of the VKOR gene as part of the present invention, the applicants were immediately in possession in all of the SNPs known in the art to exist within that sequence. It is noted that the CAFC has stated that "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Because SNPs in the VKOR gene were known in the art, even though the sequence was not previously identified as the VKOR gene, it is not necessary to recite those SNP sequences in the present specification to meet the written description requirement.

The Examiner states that the prior art, the specification and the post filing date art do not support an association between every VKOR SNP allele or mutation and warfarin sensitivity/resistance. Applicants assert that the invention as claimed does not require support for an association between warfarin sensitivity and every VKOR SNP. One of skill in the art

would readily recognize that claims 1, 3, 21 and 28 recite only those VKOR SNP alleles that are correlated with warfarin sensitivity and the specification clearly teaches one of skill in the art how such a correlation is made between any particular SNP allele of the VKOR gene and warfarin sensitivity. Thus, pursuant to the Written Description Guidelines, applicants have more than adequately demonstrated with reasonable clarity to those of skill in the art that applicants were in possession of the invention as claimed.

Thus, for at least these reasons, applicants believe the present rejection to be overcome and its withdrawal is respectfully requested.

C. The Office Action states that claims 17, 19, 22, 26, 29, 33-36, and 40-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement on the basis that they recite new matter.

Specifically, the Office Action states that claims 19, 26, 33 and 40 allegedly contain new matter in that the phrase "less than 100 base pairs in length" with regard to the amplified segment lacks support in the specification.

Applicants point out that claims 33 and 40 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims. Applicants respectfully traverse this rejection with respect to claims 19 and 26. The specification provides ample support for amplified fragments less than 100 base pairs in length. In particular, the specification discusses in Example 1 the amplification of nucleotide sequences comprising SNPs using PCR and states:

> [t]he primer pairs for each SNP are located at the upstream/downstream position of the SNP site and can generate less than 100 bp length of a DNA fragment in the PCR reaction.

(Specification, page 20, lines 19-21). Therefore, the specification provides explicit support for the phrase "less than 100 base pairs in length." Thus, claims 19 and 26 as presented herein do not contain new matter and have adequate written description. Therefore, applicants believe the present rejection of claims 19 and 26 to be overcome and respectfully request its withdrawal.

The Office Action also states that claims 22, 29, 36, and 43 allegedly contain new matter as there is insufficient support in the specification for the phrase "wherein the nucleic acid sample is from a subject in need of warfarin therapy."

Applicants point out that claims 36 and 43 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims. Applicants respectfully traverse this

rejection with respect to claims 22 and 29. Claims 22 and 29 as presented herein recite the phrase "wherein the nucleic acid sample is from a subject for whom identification of an increase or decrease in warfarin sensitivity is desired." The specification indicates that the present invention provides methods and compositions for correlating SNPs in the VKOR gene of a subject with an increased or decreased sensitivity to warfarin and that this correlation allows for more accurate and rapid determination of therapeutic and maintenance doses of warfarin at reduced risk to the subject (specification, page 2, lines 20-24). This disclosure makes it clear that the invention contemplates the determination of VKOR SNP sequences in subjects in order to determine sensitivity to warfarin and the desirability of doing so to provide safer and more accurate doses of warfarin to subjects. Thus, as discussed with Examiner Sitton during the March 4, 2009 telephone interview, the specification provides ample support for the phrase "wherein the nucleic acid sample is from a subject for whom identification of an increase or decrease in warfarin sensitivity is desired."

Applicants also note that "the invention claimed does not have to be described *in ipsis verbis* in order to satisfy the description requirement of § 112." *In re Wertheim* 541 F.2d 257, 265 (CCPA 1976). Rather, the disclosure need only reasonably convey to persons skilled in the art that the applicants had possession of the subject matter in question. *See In re Edwards*, 568 F.2d 1349, 1351-52 (CCPA 1978) ("When viewed in the context of what the parent application actually describes, the PTO has, in effect, done nothing more than argue lack of literal support. The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient.").

The present specification clearly contemplates determining warfarin sensitivity or resistance in subjects to provide safer and more accurate dosing, i.e., in subjects for whom identification of an increase or decrease in warfarin sensitivity is desired. Thus, claims 22 and 29 as presented herein do not contain new matter and have adequate written description. Therefore, applicants believe the present rejection of claims 22 and 29 to be overcome and respectfully request its withdrawal.

**III. Rejection under 35 U.S.C. § 102(e)**

The Office Action states that claims 1, 3, 20-22, 27-29, 34-36 and 41-43 are unpatentable under 35 U.S.C. §102(e) as allegedly being anticipated by Oldenberg et al. (U.S. Patent Publication No. 2005/0271644) (hereinafter "Oldenberg"). Specifically, the Office Action states that Oldenberg teaches a method of determining polymorphisms in the VKORC1 gene associated with warfarin sensitivity. The Office Action further states that, with regard to claims 1 and 3, although Oldenberg teaches specific mutations in subjects with warfarin resistance, the term "increased sensitivity to warfarin" is a relative term and depends on the comparison and that Oldenberg discloses that individuals with a C at position 292 are more sensitive to warfarin than individuals with a T at position 292. The Action further states that Oldenberg teaches subjects with specific mutations with increased resistance to warfarin, therefore needing higher doses of warfarin, and thus do not carry a SNP which imparts increased sensitivity to warfarin. The Office Action then asserts that by comparison, Oldenberg discloses 384 controls that do not carry the mutations associated with higher warfarin doses. The Office Action concludes that these controls would require lower doses than the subjects identified by Oldenberg who do not carry a SNP which imparts increased sensitivity to warfarin and further concludes that these controls meet the limitations of the claims. With regard to claims 20-22, 27-29, 34-36 and 41-43, the Office Action further states that Oldenberg teaches that genomic DNA of the human patient is isolated and the coding sequence amplified by PCR primers, and that Oldenberg teaches detecting polymorphisms and PCR amplification in subjects in need of warfarin therapy.

As an initial matter, applicants note that claims 34-36 and 41-43 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

Applicants submit that the earliest available priority date for Oldenberg et al. is October 14, 2003 based on a provisional application filed on that date. Applicants will provide to the Examiner a Declaration under 37 C.F.R. § 1.131 that provides evidence of the conception and reduction to practice of the present invention that warrants removal of this reference as available art against the presently claimed invention. Thus, applicants believe this rejection to be overcome and its withdrawal is respectfully requested.

Applicants further respectfully traverse this rejection on additional bases. In particular, as discussed with Examiner Sitton and her supervisor, Examiner Shukla, during the September

25, 2007 interview, Oldenberg does not teach a method of identifying a human subject having an increased sensitivity to warfarin, as set forth in claims 1 and 3. Furthermore, claims 20-22 and 27-29 depend from claims 18 and 25, respectively, which recite amplifying segments from the noncoding regions of the VKOR genomic nucleotide sequence. As discussed with Examiner Sitton during the March 17, 2009 telephone interview, Oldenberg fails to teach or suggest the amplification of non-coding regions of the VKOR genomic nucleotide sequence

To the extent that the Examiner relies upon the disclosure of Oldenberg as teaching increased warfarin sensitivity, the applicants respectfully submit that the Office Action misinterprets and misapplies the definition of warfarin sensitivity as set forth in the present application. As one of ordinary skill in the art would readily understand, within any population there are subjects that require maintenance dosage levels of warfarin that fall within a range that is considered "normal." Thus, there exist patients that are "normal" and would not be classified only as either "sensitive" or "resistant," as is the implication in the Office Action. A normal therapeutic or maintenance dosage range for warfarin is generally understood to be typically 4-6 mg/day. (*See,* e.g., references 1-4 below). Those patients requiring more warfarin than the average maintenance dose to keep their blood from coagulating are considered resistant and those that require less warfarin because at the normal dose they exhibit such life-threatening side effects as hemorrhaging are considered sensitive. In addition, there is also a base population for which the "normal" dosage levels are appropriate. Thus, as the ordinary skilled artisan would understand, the "absence of mutations for resistance" does not necessarily mean that such a subject has increased sensitivity to warfarin as such a patient could also fall within a normal dosage range for that population. In further support of this contention, applicants bring to the Examiner's attention the publication by Scott et al. (*Am. J. Hum. Genet.* 82:495-500 (2008); reference 5 below), in which these investigators report that the VKOR allele g.-1639G is associated with a "normal" warfarin dose, while g.-1639A allele is associated with warfarin sensitivity (*Id* at paragraph bridging pages 496-497). Thus, it is clear that one of skill in the art would not reasonably understand that the absence of a mutation for resistance necessarily means that such a subject would have increased sensitivity to warfarin.

Accordingly, warfarin sensitivity and warfarin resistance are not relative terms as the Examiner contends, but rather are terms that are well understood by one of ordinary skill in the

art to be based on a patient's response to the average therapeutic dose of warfarin. Therefore, one of ordinary skill in the art would readily understand that there are patients that respond appropriately to the normal or average dose of warfarin with the desired level of anticoagulation and there are others who do not. Of the patients that do not respond appropriately, there are those that hemorrhage at the normal doses of warfarin and these patients would be considered sensitive. Patients that do not achieve the level of anticoagulation desired until they receive higher than normal doses of warfarin would be considered resistant. The following references support this contention as they set forth what one of ordinary skill in the art would understand regarding normal dosages of warfarin and the expression of warfarin sensitivity in a patient (a copy of each is enclosed).

(1) Horton et al. "Warfarin therapy: evolving strategies in anticoagulation"; *American Family Physician* 59(3):635-46 (Feb. 1, 1999) (*See,* paragraph six under section entitled "Pharmacodynamics and Dosing Considerations" wherein it is stated that "[i]n most patients, the average maintenance dose is 4 to 6 mg per day.").

(2) Gage et al. "Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin." *Thromb. Haemost.* 91:87-94 (2004) (*See,* page 89, last paragraph, wherein it is stated that "[t]he arithmetic mean dose was 5.2 mg/day and the geometric mean was 4.6 mg/day.")

(3) Reider et al. "Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose," *New Engl. J Med.* 353:2285-2293 (2005) (*See*, page 2290, first full paragraph, wherein it is stated that "[i]n the primary population, the overall mean dosage of warfarin (5.1+/-0.2mg per day) and range of maintenance doses were typical of those that have been reported in other clinical studies.") For other clinical studies, Reider et al. cites to the Gage et al. study cited above.

(4) Taube et al. "Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-coagulation in patients on long-term treatment." *Hemost Thromb Vasc. Biol.* 96(5);1816-1819 (2000)) (*See,* page 1818, second column, second paragraph, which discusses that the Aithal et al.

study defined sensitive patients as having a warfarin dose requirement of 1.5 mg or less; Taube et al. also adopted this definition as a parameter of warfarin sensitivity).

(5) Scott et al. "Warfarin Pharmacogenetics: CYP2C9 and VKORC1 genotypes predict different sensitivity and resistance frequencies in the Ashkenazi and Sephardi Jewish populations." *Am. J. Hum. Genet.* 82:495-500 (2008). (See above discussion.)

Thus, the methods of the rejected claims are not anticipated by Oldenberg. Therefore, applicants submit that the present rejection is overcome and respectfully request its withdrawal.

**IV. Rejection under 35 U.S.C. § 102(a)**

The Office Action states that claims 1, 3, 20-22, 27-29, 34-36 and 41-43 are unpatentable under 35 U.S.C. §102(a) as allegedly being anticipated by Rost et al. (*Nature* 427:537-541 (2004)) (hereinafter "Rost"). Specifically, the Office Action asserts that Rost teaches a method of determining polymorphisms in the VKOR gene associated with warfarin resistance. The Office Action further states that, with regard to claims 1 and 3, although Rost teaches specific mutations in subjects with warfarin resistance, the term "increased sensitivity to warfarin" is a relative term and depends on the comparison and that Rost teaches subjects with specific mutations with increased resistance to warfarin, therefore needing higher doses of warfarin, and thus do not carry a SNP which imparts increased sensitivity to warfarin. The Office Action additionally states that by comparison, Rost further teaches that 384 controls do not carry the mutations associated with higher warfarin doses and thus the Office Action concludes that these control subjects require lower doses than the subjects identified by Rost who do not carry a SNP allele which imparts increased resistance to warfarin. From this, the Office Action further concludes that these controls meet the limitation of the claims. With regard to claims 20-22, 27-29, 34-36 and 41-43, the Office Action further states that Rost teaches that genomic DNA of the human patient was isolated and the coding sequence amplified by PCR using primers, and that Rost teaches detecting polymorphisms and PCR amplification in subjects in need of warfarin therapy.

As an initial point, applicants note that claims 34-36 and 41-43 are canceled herein

without prejudice, thereby mooting this rejection as it pertains to these claims

Applicants submit that the earliest available priority date for Rost et al. is February 4, 2004. Applicants will provide to the Examiner a Declaration under 37 C.F.R. § 1.131 that provides evidence of the conception and reduction to practice of the present invention that warrants removal of this reference as available art against the presently claimed invention. Thus, applicants believe this rejection to be overcome and its withdrawal is respectfully requested.

Applicants further respectfully traverse this rejection citing Rost et al. as teaching warfarin sensitivity on the same bases discussed above regarding Oldenberg.

It is also noted that the Office Action states that further support that the relativity of the terms warfarin sensitivity and warfarin resistance can be based on a comparison is provided in the teaching by Rost that "sensitive" rats were homozygous for tyrosine at position 139 whereas "resistant" rats were homozygous and heterozygous, respectively for the Tyr139Cys mutation. Applicants respectfully disagree with this interpretation of Rost et al.

Specifically, it is noted that the "sensitive" rats in Rost are "wild-caught rats" that were not resistant to warfarin used as a rodenticide. Oldenberg discusses the fact that warfarin had been used as a rodenticide since the 1950s but that over time the use of this compound as a rodenticide resulted in populations of rats developing resistance (Oldenberg, para 0011). Clearly, using a compound to kill an organism is a completely different application from trying to adjust the dosage of a compound in patient so that the dosage is sufficient to accomplish the result of reduced blood coagulation but not so high as to result in hemorrhaging. Thus, what is defined as a resistant versus sensitive rat in Rost would not be understood by a person of ordinary skill to be relevant to the definition of warfarin sensitivity or resistance in a human patient. There is no consideration in the discussion in Rost for a population that is "normal" in the sense that such a population can receive a normal dose of warfarin and at the same time avoid blood clots and hemorrhaging. Further, Rost does not teach or suggest SNPs associated with warfarin sensitivity. Accordingly, Rost fails to teach each and every recitation of the rejected claims and thus fails to anticipate these claims. Therefore, applicants believe the present rejection to be overcome and respectfully request its withdrawal.

**V. Rejections under 35 U.S.C. § 103(a)**

**A.** The Office Action states that claims 3-5 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Oldenberg et al. in view of Aithal et al. (*The Lancet* 353: 717-719 (1999)) (hereinafter "Aithal"). Specifically, the Office Action states that Aithal teaches identifying patients with a warfarin dose requirement of 1.5 mg or less, detecting polymorphisms in the CYP2C9 gene and correlating the genotype with warfarin sensitivity. The Office Action thus concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screen the VKOR gene in human subjects for additional SNPs associated with different warfarin dose requirements as taught by Oldenberg. The motivation suggested in the Office Action for one of ordinary skill in the art to screen for additional SNPs in the VKOR gene associated with warfarin dose requirements is that Oldenberg teaches that vitamin K epoxide reductase is a component of the vitamin K cycle which is targeted by coumarin.

As noted above, claims 4 and 5 are canceled herein, thereby mooting this rejection as it pertains to these claims.

As discussed above, the earliest available priority date for Oldenberg et al. is October 14, 2003 based on a provisional application filed on that date. Applicants will provide to the Examiner a Declaration under 37 C.F.R. § 1.131 that provides evidence of the conception and reduction to practice of the present invention that warrants removal of this reference as available art against the presently claimed invention. Thus, applicants believe this rejection to be overcome and its withdrawal is respectfully requested.

However, the applicants further respectfully traverse this rejection on additional bases. Specifically, as stated in the recently published Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.*...." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some

**suggestion or incentive that would have motivated** the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a **reasonable expectation of success**, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references **must teach or suggest all of the limitations of the claims**. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Therefore, even if Oldenberg were available as a reference, as discussed above, Oldenberg fails to provide incentive to carry out a method of correlating an allele of SNP in the VKOR gene of a human subject with increased sensitivity to warfarin. At most, Oldenburg discusses SNPs in the coding region of the VKOR gene that are related to warfarin resistance only, and the secondary reference, Aithal, fails to remedy these deficiencies of Oldenberg.

Aithal teaches only variant alleles of cytochrome P450 CYP2C9 and the association of these variant alleles with warfarin sensitivity. Aithal does not provide incentive to look at the VKOR gene or any association of the VKOR gene with warfarin sensitivity. Until the discovery by the present inventors of SNP alleles in the VKOR gene that are associated with warfarin sensitivity, even if one were motivated to examine VKOR SNP alleles, there would have been no expectation of success or predictability in discovering SNP alleles in the VKOR gene associated with sensitivity to warfarin dosage. This is because, as far as the skilled artisan would have been aware at the time the present invention was made, the only alleles associated with increased sensitivity to warfarin dosage had been identified in the CYP2C9 gene and for VKOR, only SNP alleles associated with warfarin resistance had been identified, and those were only in the coding region. Thus, to the extent that one of ordinary skill in the art could have had any expectations regarding an association of an allele of a SNP of the VKOR gene, such a skilled person would only have reasonably expected that polymorphisms of the VKOR gene only were associated with warfarin resistance.

Accordingly, prior to the applicants' own discovery, one of ordinary skill in the art would

not have had any reasonable expectation of success or predictability in identifying SNP alleles of the VKOR gene associated with warfarin sensitivity based on this combination of references. Therefore, applicants submit that the present rejection is overcome and respectfully request its withdrawal.

**B.** The Office Action states that claims 3-5 are allegedly unpatentable under 35 U.S.C. §103(a) over Rost et al. in view of Aithal (*The Lancet* 353: 717-719 (1999)).

As noted above, claims 4 and 5 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

As discussed above, the earliest available priority date for Rost et al. is February 4, 2004. Applicants will provide to the Examiner a Declaration under 37 C.F.R. § 1.131 that provides evidence of the conception and reduction to practice of the present invention that warrants removal of this reference as available art against the presently claimed invention. Thus, applicants believe this rejection to be overcome and its withdrawal is respectfully requested.

Applicants further respectfully traverse this rejection on additional bases. Even if Rost were available as a reference, as discussed above, Rost fails to teach or suggest a method of correlating an allele of a SNP in the VKOR gene of a human subject with increased sensitivity to warfarin. At best, Rost discusses SNPs in the VKOR gene that are related to warfarin resistance only. For the same reasons as set forth above for Oldenberg, Aithal fails to remedy the deficiencies of Rost. Accordingly, applicants respectfully submit that the present rejection is overcome and respectfully request its withdrawal.

**C.** The Office Action states that claim 17 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Oldenberg et al. or Rost et al., each in view of Aithal and in further view of Risch (*Nature* 405:847-856 (2000)).

As noted above, claim 17 is canceled herein, thereby mooting this rejection. Thus, applicants respectfully request the withdrawal of this rejection.

**D.** The Office Action states that claims 18-21 and 25-28 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over ss1516544 (dbSNP rs7294, build 86:10/16/2000) or in the alternative ss12359507 (dbSNP rs8050894, build 116:8/7/2003) each in view of Oefner (U.S. Patent No. 6,453,244). Specifically, the Office Action states that ss1516544 teaches a G/Z SNP in a VKOR genomic sequence which corresponds to position 4769 of SEQ ID NO: 11 but

does not teach how to detect the SNP. The Office Action further states that ss12359507 teaches a C/G SNP in a VKOR genomic sequence which corresponds to position 2581 of SEQ ID NO: 11 but does not teach how to detect the SNP. The Office Action states that Oefner teaches a method of detecting polymorphisms and that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long. The Office Action alleges that it would have been obvious to use the method of Oefner to detect mutations/polymorphisms in the genomic nucleic acid sequences taught by ss1516544 or ss12359507 and that one would be motivated to do so because Oefner teaches it is an effective method to detect allelic variants in nucleic acid sequences.

Applicants respectfully traverse this rejection. A review of the GenBank® listing associated with the cited document shows that ss1516544 discloses a nucleotide sequence from a very small (50 nucleotide) portion of a cDNA (not a genomic sequence as stated in the Office Action) isolated from a multiple sclerosis lesion. The sequence disclosed in ss1516544 is not identified, nor is it even disclosed whether it is a coding or noncoding sequence. Thus, in contrast to the statement in the Office Action, ss1516544 does not disclose an identified VKOR sequence, it simply discloses a sequence of unknown function comprising a SNP of unknown value.

Similarly, a review of the GenBank® listing associated with the cited document shows that ss12359507 discloses a nucleotide sequence from a small portion of chromosome 16. The sequence disclosed in ss12359507 is not identified, nor is it even disclosed whether it is a coding or noncoding sequence. Thus, in contrast to the statement in the Office Action, ss12359507 does not disclose an identified VKOR sequence, it simply discloses a sequence of unknown function comprising a SNP of unknown value.

Oefner teaches a general technique for detecting polymorphisms in a nucleic acid (see abstract). Oefner does not point to any particular sequence or SNP to be tested or detected.

In the present Office Action the Examiner states that one of ordinary skill in the art would have been motivated to apply the method of Oefner to the disclosed sequences because the Oefner method is effective to detect allelic variants. However, the Office Action fails to state why one would be motivated to detect these particular allelic variants.

"[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead,

there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385, 1396 (2007) quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396.

Claim 18 as presented herein recites a method of amplifying a segment of a VKOR genomic nucleotide sequence, wherein said segment is in a noncoding region of the nucleotide sequence, comprising: a) choosing a first oligonucleotide primer from the 3′ end of the nucleotide sequence of SEQ ID NO:8; b) choosing a second oligonucleotide primer from the 5′ end of the nucleotide sequence of SEQ ID NO:8; c) adding said first primer and said second primer to a nucleic acid sample; and d) amplifying a segment of the VKOR genomic nucleotide sequence defined by the first primer and the second primer, wherein said segment is in a noncoding region of the nucleotide sequence.

Claim 25 as presented herein recites a method of amplifying a segment of a VKOR genomic nucleotide sequence, wherein said segment is in a noncoding region of the nucleotide sequence, comprising: a) choosing a first oligonucleotide primer from the nucleotide sequence of SEQ ID NO:8; b) choosing a second oligonucleotide primer from the nucleotide sequence of SEQ ID NO:8 that differs in nucleotide sequence from the first oligonucleotide primer; c) adding said first primer and said second primer to a nucleic acid sample; and d) amplifying a segment of the VKOR genomic nucleotide sequence defined by the first primer and the second primer, wherein said segment is in a noncoding region of the nucleotide sequence.

The two SNP sequences disclosed in the cited references are located in sequences of unknown function and the SNPs are of unknown value. Out of the thousands of SNPs that had been identified in the human genome as of the effective filing date of the present application, the Office Action has provided no reason, either in the cited references or in the general knowledge in the art, why the ordinarily skilled artisan would choose to amplify either one of the cited SNPs.

The Court of Customs and Patent Appeals held in *In re Stemniski*, 444 F.2d 581 (C.C.P.A. 1971) that a claimed compound could not be obvious over similar prior art compounds

if there was no known utility for the prior art compounds. The court stated that:

> [a] discovery of an unexpected utility for a novel compound is evidence directly relevant to the issue of the unobviousness of the compounds claimed over those of the prior art. Where as here, the utility discovered is not disclosed, taught or suggested for the prior art compounds but in fact the art is silent on any utility for the prior art compounds, the discovery of the utility itself is evidence of the unobviousness of the novel compounds.

*Stemniski* at 584.

The court further asked:

> What on this record – other than abstract, theoretical or academic considerations – would lead one of ordinary skill to change the structure of the reference compounds to obtain the claimed compounds? Certainly no practical considerations which promote the progress of useful art or are of use to society are manifest. How can there be obviousness of structure, or particularly of the subject matter as a whole, when no apparent purpose or result is to be achieved, no reason or motivation to be satisfied, upon modifying the reference compounds' structure?

*Stemniski* at 584.

The present situation is analogous to *Stemniski*. The respective SNPs disclosed in the cited references had no known utility as they were not present in a known gene and were not linked to any function. Of further relevance is the fact that the Court of Appeals of the Federal Circuit (CAFC) found in *In re Fisher* (421 F.3d 1365 (Fed. Cir. 2005) that expressed sequence tags to unknown genes had no substantial utility for identifying polymorphisms in the unknown gene as the polymorphisms would provide little information. *Fischer*, 421 F.3d at 1368. Although *Fisher* relates to a utility rejection, it clearly shows that identification of a polymorphism (SNP) of unknown value in a sequence of unknown function has no utility. *Fisher* further states that issues of utility apply with equal force in the fields of chemistry and biology (*Fischer*, 421 F.3d at 1375), showing that the reasoning of *Stemniski* (that it cannot be obvious to modify a compound having no known utility) applies to the present application. Even though the SNPs could be detected by the method of Oefner, this fact alone is insufficient to render the claims obvious as there is no reason why one would be motivated to amplify a SNP having no known utility. Applicants have discovered a utility for the SNPs of this invention and thus a reason for amplifying the SNPs and this discovery is evidence of the unobviousness of the claimed method. Furthermore, the CAFC recently stated that, even when a polynucleotide

sequence is anticipated by the prior art, a new method of using the polynucleotide will be patentable. *In re Gleave*, 2009 U.S. App. LEXIS 6389, 18).

Thus, the methods of claims 18-21 and 25-28 as presented herein are not obvious over ss1516544 or in the alternative ss12359507, each in view of Oefner. Therefore, applicants believe this rejection to be overcome and respectfully request its withdrawal.

**E.** The Office Action states that claims 18-21, 25-28, 32-35, and 39-42 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lyman (WO 99/33983) in view of Oefner (U.S. Patent No. 6,453,244). Specifically, the Office Action states that Lyman teaches a nucleic acid molecule which is identical to positions 48-539 of SEQ ID NO: 9, which sequence comprises allelic variants. The Office Action notes that Lyman does not teach how to detect allelic variants. The Office Action goes on to state that Oefner teaches a method of detecting polymorphisms and that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long. The Office Action alleges that it would have been obvious to use the method of Oefner to detect mutations/polymorphisms in the nucleic acid sequences taught by Lyman and that one would be motivated to do so because Oefner teaches it is an effective method to detect allelic variants in nucleic acid sequences.

As an initial matter, claims 32-35 and 39-42 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

Applicants respectfully traverse this rejection. Lyman discloses a nucleotide sequence from an unknown cDNA encoding an unknown protein. The sequence of the cDNA was not found to be highly related to any other known sequences. Lyman, page 6, lines 5-6. While Lyman states that the invention encompasses nucleic molecules that are allelic variants of SEQ ID NO: 1 (page 4, lines 10-11), no actual allelic variants are disclosed. Thus, Lyman simply discloses a sequence of unknown function with no known SNPs.

Oefner teaches a general technique for detecting polymorphisms in a nucleic acid (see abstract). Oefner does not point to any particular sequence or SNP to be tested or detected.

The Office Action states that one of ordinary skill in the art would have been motivated to apply the method of Oefner to the disclosed sequence of Lyman because the Oefner method is effective to detect allelic variants. However, the Office Action fails to state why one would be motivated to look at the particular sequence of Lyman, why one would expect there to be SNPs

present in the Lyman sequence to be identified, or why identification of any SNPs in the Lyman sequence would be useful. The Office Action has provided no reason, either in the cited references or in the general knowledge in the art, why the ordinarily skilled artisan would choose to amplify the Lyman sequence or why one would have a sufficient expectation that the Lyman sequence contains a SNP such that the Oefner technique should be applied to the sequence.

The present situation relating to this rejection based on Lyman is analogous to *Stemniski* as discussed above for the previous rejection. In particular, the nucleic acid sequence disclosed in Lyman had no known utility related to SNPs or even to the biological function of the sequence. In fact, it is stated in Lyman that the V201 polypeptide is "probably a growth factor" (page 6, lines 8-9) and that the V201 polypeptide can be useful "as a therapeutic agent in inhibiting IL-1 and TNF signaling" (page 32, line 10) and as a reagent "in the study of the IL-1 signaling pathway as a reagent to block Il-1 signaling." (page 32, line 32). Thus, to the extent that Lyman provides any suggestion about the utility of the V201 polypeptide or nucleic acid encoding it, such suggestions would actually direct one of skill in the art away from any motivation to amplify any SNPs that may be present for any reason associated with a VKOR gene and certainly not for the purpose of correlating SNP alleles with warfarin sensitivity.

Furthermore, as also noted above, the relevance of *In re Fisher* and *In re Gleave* applies equally to the present rejection. Even though any SNPs present in the Lyman sequence could have been detected by the method of Oefner, this fact alone is insufficient to render the claims obvious as there is no reason why one would be motivated to detect a SNP having no known utility. Applicants have discovered a utility for the SNPs and a reason for amplifying the SNPs and this discovery is evidence of the unobviousness of the claimed method. Thus, neither Lyman nor Oefner, alone or in combination, teach or suggest the recitations of the presently claimed invention. Therefore, applicants believe the present rejection is overcome and respectfully request its withdrawal.

**F.** The Office Action states that claims 23, 24, 30, and 31 are rejected under 35 U.S.C. §103(a) as unpatentable over ss1516544 or in the alternative ss12359507 each in view of Oefner and further in view of Keller and Manak (*DNA Probes,* 2nd Ed, 1993, Macmillan Publishers Ltd., page 259). Specifically, the Office Action states that ss1516544, ss12359507, and Oefner are applied as set forth above but do not teach primer lengths. The Office Action further states that

Keller and Manak teaches that PCR primers are typically 15-30 nucleotides long and that it would have been *prima facie* obvious to utilize primers that are at least 15 nucleotides long in the method of ss1516544, ss12359507, and Oefner.

Applicants respectfully traverse this rejection. As discussed above, no motivation or incentive is found in ss1516544, ss12359507, and Oefner or in the general knowledge in the art to amplify the sequences disclosed in ss1516544 or ss12359507 using the method of Oefner, because the disclosed sequences and SNPs have no known identity or function. The Keller and Manak reference does not remedy the deficiencies of the other cited references. Keller and Manak is a textbook that generally describes the PCR technique and provides no motivation or incentive to apply PCR to the sequences disclosed in ss1516544 or ss12359507.

Thus, the methods of claims 23, 24, 30, and 31 as presented herein are not obvious over ss1516544 or in the alternative ss12359507 each in view of Oefner and further in view of Keller and Manak. Therefore, applicants believe the present rejection to be overcome and respectfully request its withdrawal.

**G.** The Office Action states that claims 23, 24, 30, 31, 37, 38, 44, and 45 are rejected under 35 U.S.C. §103(a) as unpatentable over Lyman in view of Oefner and further in view of Keller and Manak, all of which are described above.

As an initial matter, claims 37, 38, 44, and 45 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

Applicants respectfully traverse this rejection. As discussed above, no motivation or incentive is found in Lyman and Oefner or in the general knowledge in the art to amplify the sequence disclosed in Lyman using the method of Oefner, because the disclosed sequence has no known identity or function and is not known to contain any SNPs. The Keller and Manak reference does not remedy the deficiencies of the other cited references. Keller and Manak is a textbook that generally describes the PCR technique and provides no motivation or incentive to apply PCR to the sequence disclosed in Lyman.

Thus, the methods of claims 23, 24, 30, 31, 37, 38, 44, and 45 as presented herein are not obvious over Lyman in view of Oefner and further in view of Keller and Manak. Therefore, applicants believe the present rejection to be overcome and respectfully request its withdrawal.

**H.** The Office Action states that claims 19, 26, 33 and 40 are rejected under 35 U.S.C.

§103(a) a being unpatentable over Oldenberg or Rost, each in view of Oefner. Specifically, the Office Action states that Oldenberg and Rost are applied as set forth above but do not teach producing an amplicon that is 100 base pairs or less. The Office Action further states that Oefner teaches a method of detecting polymorphisms involving PCR amplification and that the nucleic acid oligomers to be analyzed are preferably from 40-90 nucleotides long and that it would have been *prima facie* obvious to use the method of Oefner to detect mutations/polymorphisms in the method of Oldenberg or Rost.

As an initial matter, claims 33 and 40 are canceled herein without prejudice, thereby mooting this rejection as it pertains to these claims.

Applicants respectfully traverse this rejection. As discussed above, applicants will provide to the Examiner a Declaration under 37 C.F.R. § 1.131 that provides evidence of the conception and reduction to practice of the present invention that warrants removal of both Oldenberg and Rost as available art against the presently claimed invention. Thus, applicants believe this rejection to be overcome and its withdrawal is respectfully requested.

Applicants further respectfully traverse this rejection on additional bases. Claims 19 and 26 depend from claims 18 and 25, respectively, and relate to amplifying segments from the noncoding regions of the VKOR genomic nucleotide sequence, wherein the amplified segment is less than 100 bases in length.

Both Oldenberg and Rost fail to teach or suggest the amplification of <u>non-coding regions</u> of the VKOR genomic nucleotide sequence as taught by the present invention. Oefner teaches a general technique for detecting polymorphisms in a nucleic acid (see abstract). Oefner does not point to any particular sequence or SNP to be tested or detected.

The Office Action states that one of ordinary skill in the art would have been motivated to apply the method of Oefner to the SNPs disclosed in Oldenberg or Rost because the Oefner method is effective to detect allelic variants. However, the Office Action fails to state why one would be motivated to amplify the non-coding regions of the VKOR genomic nucleotide sequence to search for SNPs in view of the teachings of Oldenberg and Rost that SNPs related to warfarin resistance are present in the coding region of VKOR. Therefore, the Examiner has failed to make a *prima facie* case of obviousness.

Thus, the methods of claims 19, 26, 33 and 40 as presented herein are not obvious over

Oldenberg or Rost, each in view of Oefner. Therefore, applicants believe the present rejection to be overcome and respectfully request its withdrawal.

Having addressed all of the issues raised in the present Office Action, the applicants respectfully submit that all of the claims of this application are in condition for allowance, which action is respectfully requested. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the allowance of the pending claims to issue.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of **$940.00** ($130.00 as fee for a one month extension of time and $810.00 as fee for a Request for Continued Examination (RCE)). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency associated with this filing or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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**CERTIFICATION OF TRANSMISSION**

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on April 28, 2009.

Claire Wimberly

Claire Wimberly